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Prostate cancer genetics and biology: literature review

Relevance: *Despite a high survival with localized prostate cancer, metastatic prostate cancer remains virtually incurable even after intensive multimodal therapy. Death in advanced stages of the disease is caused by the lack of therapeutic regimens able to produce a long-term tumor reaction due to its extreme genetic and cellular heterogeneity. According to epidemiological studies, a family history of prostate cancer significantly increases the risk. Clinical diagnosis is often based on a single biopsy made to determine a particular cancer case molecular status. Pathological and genomic heterogeneity can lead to bias in diagnosis. Therefore, the use of genetic research technologies is highly relevant.*

The study aimed to justify the use of genetic profiling technologies for patients with prostate cancer.

Results: *Many cases lack an understanding of the multifactorial impact of current treatment methods on the patient's immune system. Combination therapy efficacy and tolerability depend on the choice of an optimal treatment regimen. Approaches to prioritizing the types of combination therapy should be developed. The cancer genome affects the disease course and progression. Simulation of these interactions in a genetic model allows predicting the treatment outcome and effectiveness.*

Conclusions: *The conducted systematic review shows that a deep understanding of prostate cancer biology and genetics and genetic profiling can save and improve the lives of many patients with serious diseases.*

Keywords: Prostate cancer, tumor heterogeneity, tumor microenvironment, genetic profiling.

Introduction: Nowadays, prostate cancer ranks sixth in prevalence and second among malignant diseases in men worldwide; in some countries, it is the most common cancer [1, 2]. The number of new prostate cancer cases registered annually amounted to 1 million in 2012 and 1.2 million in 2018 [3] and is expected to reach 1.7 million by 2030, with a mortality rate of about 500,000 worldwide [4]. Many prostate cancer studies show its significant prevalence in Western countries [5], with an overwhelming majority of cases in North America and Europe. Prostate cancer incidence in Asian countries is significantly lower these days [6]. Some authors associate this difference with social and cultural characteristics and life expectancy since prostate cancer incidence has increased in some Asian countries in the course of their economic and social development [7]. Perhaps, low prostate cancer incidence in Asia compared to the Western world is due to inadequate screening and diagnostics. There are also studies regarding behavioral features, such as nutrition, physical activity, and the use of various substances.

The study aimed to justify the use of genetic profiling technologies for patients with prostate cancer.

Materials and Methods: The PubMed, Medline, and Cochrane databases were studied for articles by keywords "prostate cancer," "tumor heterogeneity," "tumor microenvironment," and "genetic predictors." The total number of articles amounted to 2,900, or 2,748,

after the removal of duplicates. One thousand eight hundred fifty full-text publicly available articles were selected for analysis. Thirty-seven reviews were included in the qualitative synthesis after screening for acceptability.

Results and Discussion: A series of papers emphasize genetic and environmental factors, including geographical factors, due to the difference in prostate cancer distribution in European and Asian countries [8-10]. Many studies of twins and genome-wide associations (GWAS) revealed genetic determinants existing in prostate cancer etiology. Epidemiological studies have shown that a family history of malignant prostate diseases significantly increases prostate cancer risk [11, 12]. For example, a single nucleotide polymorphism (SNP) rs339331 enhances the expression of the RFX6 gene, which increases cancer risk by interacting with the HOXB13, BRCA2, ATM, CHEK2, BRCA1, RAD51D, and PALB2 genes [13-15]. Several large genomic trials of prostate tumors have revealed the repeated changes of DNA copy numbers and gene mutations, restructuring, and fusion [16]. The newly diagnosed prostate cancer is a multicentric disease with significant heterogeneity. Thus, a thorough pathological review of a sample of biological material is crucial for diagnosis. Recent research showed that primary prostate cancer foci could have G84E HOXB13 mutations that increase the risk of prostate cancer development [17]. Boutros et al. performed genomic sequencing of mul-

multiple lesions in individual patients to evaluate primary prostate cancer molecular heterogeneity. They found new changes, including recurring focal amplification of MYCL and MYC genes, as well as known recurrent changes, including loss of NKX3.1 and TP53. A foreign paper on multifocal tumors genome sequencing described mutations in 16 genes, including BRCA2, ATM, CHEK 2, BRCA1, RAD51D, and PALB2 [18].

In many cases, clinical diagnosis is often based on a single biopsy made to determine a particular cancer case molecular status. Pathological and genomic heterogeneity can result in systematic errors in diagnosis. Gundems et al. performed whole-genome sequencing of 51 multifocal primary and metastatic tumors in 10 patients to characterize the subclonal tumor architecture. They found that metastases originated from multiple clones transported between different metastatic sites or one daughter clone originating from another metastatic site [19].

The prostate tumors' heterogeneity is often manifested at the functional level in the cancer cell population, especially regarding the differentiation status. However, the role of stem tumor cells remains unclear. Multipotent stem and progenitor cells found in an unchanged prostate gland could give rise to basal and endocrine cells [20]. The mouse prostate gland clone studies showed that basal cells could give rise to prostate tumors, and differentiation regulation disorder is critical in basal cell type prostate cancer initiation [21]. For example, the BMI1 proto-oncogene critical role in regulating prostate stem cell renewal and tumor initiation was established [22, 23].

Significant intratumoral heterogeneity is present in cell-type diversity and an extracellular matrix composition comprising the tumor microenvironment. This microenvironment includes tumor-associated fibroblasts, mesenchymal stem cells, and immune cells. The microenvironment composition plays an important role in regulating tumor cell proliferation, angiogenesis, metastasis, and resistance to therapeutic agents [24, 25]. The tumor microenvironment heterogeneity is manifested in cell composition and the differences in cell phenotype and functional status.

Lymphocytes are the known key cellular components of the adaptive immune system that protect from infectious pathogens. However, some lymphocyte subtypes also play a central role in cancer development and containment [26]. Some studies evaluate the association between lymphocytic infiltration and clinical parameters, such as the tumor development stage. For example, the correlation of CD4 and helper T cells, CD8 and cytotoxic T cells, CD4 with FOXP3,

and regulatory T cells in tumor tissue with inflammation and various types of atrophies was analyzed [27]. The studies showed that the complex CD4 + Tregs, but not CD4 + T-helper or CD8 + cytotoxic T-cells, was associated with an increased risk of mortality. Moreover, an increase of CD20 and B-cell levels inside the tumor was observed in tumors with a high risk of relapse or progression [28]. However, these immune profiles should be interpreted carefully, with checking the immune cell subtype, heterogeneity within immune cell subtypes, and the immune cells functional state, to enhance such profiles' predictive power regarding clinical outcomes. All these studies were conducted in primary prostate tumors so far, highlighting the need for a similar study of prostate cancer metastatic spread.

Other most common nucleus-containing cells in the body, myeloid cells, are necessary for the normal function of both the innate and adaptive immune systems. They and tumor-related macrophages are important regulators of tumor progression, metastasis, and resistance to treatment. Suppressor cells of myeloid origin include a population of immature myeloid cells that accumulate in pathological conditions such as cancer due to incomplete blocking of the immunological program [29]. Suppressor cells of myeloid origin express markers such as CD11b and CD33, but mostly negative against antigens D associated with the leukocyte antigen and such antigens as CD3, CD19, and CD57 [30]. Suppressor cells of myeloid origin can be divided into PMN-MDSC and M-MDSC and have a significant immunosuppressive activity [30]. Some authors believe in a major role these suppressor cells have in suppressing the immune response in primary cancer, tumor cell invasion, and metastasis [31, 32].

Today, the development of effective and targeted prostate cancer treatment methods is still an issue. In many cases, there is no profound understanding of the impact of the existing treatment methods on the patient's immune system. Combination therapy efficacy and tolerability should be achieved by optimizing dosing regimens. Approaches shall be developed to prioritize different types of combination therapy. Considering that the cancer genome affects the disease course and progression, these interactions could be simulated in a genetic model to predict the treatment outcome and efficacy.

Conclusions: Often, clinical diagnosis is often based on a single biopsy made to determine the tumor molecular status. Pathological and genomic heterogeneity can result in systematic errors in diagnosis. This proves the need to improve genetic examination methods for patients with different forms of prostate

cancer. A deep understanding of prostate cancer biology and genetics and the development of genetic profiling provide an opportunity to preserve and improve the lives of many patients with serious diseases.

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ТҰЖЫРЫМ

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Қуықасты безі қатерлі ісігінің генетикасы және биологиясы

Өзектілігі: Қуықасты безінің локализацияланған қатерлі ісігі кезінде ұзақ уақыт өмір сүруге қарамастан, қуықасты безінің метастатикалық қатерлі ісігі қарқынды мультимодальды терапиядан кейін де іс жүзінде емделмейтін болып қалады. Асқынған аурудан болатын өлім-жітім генетикалық және жасушалық биологиялық деңгейлерде ісіктің аса гетерогендігі жағдайында ұзақ реакция тудыруға қабілетті терапиялық схемалардың жоқтығынан туындайды. Анықталған эпидемиологиялық зерттеулер қуықасты безінің қатерлі ауруларының отбасылық анамнезі тәуекелді едәуір арттыратынын көрсетті. Көптеген жағдайларда клиникалық диагноз қатерлі ісіктің нақты жағдайының молекулалық мәртебесін анықтау үшін жалғыз биопсияға негізделеді. Патологиялық және геномдық гетерогендікке байланысты диагноз қою кезінде жүйелі қателер туындауы мүмкін.

Зерттеудің мақсаты: Қуықасты безінің қатерлі ісігі бар пациенттерге қатысты генетикалық бейіндеу технологияларын қолдануды негіздеу.

Нәтижелері: Көптеген жағдайларда қолданыстағы емдеу әдістерінің пациенттің иммундық жүйесіне әсерін жан-жақты түсіну жоқ. Құрамдастырылған терапиямен байланысты тиімділігі мен төзімділігі емдеуді мөлшерлеу режимдерін оңтайландыру жолымен анықталуы тиіс және құрамдастырылған терапияның әртүрлі түрлерінің басымдықтарын анықтау үшін тәсілдерді әзірлеу қажет болуы мүмкін. Қатерлі ісіктің геномы аурудың үдеуі мен ағымына әсер ететінін ескере отырып, генетикалық модель жағдайында осы өзара іс-қимылдарды модельдеу мүмкін, бұл жүргізілген емдеудің нәтижесі мен тиімділігін болжауға мүмкіндік береді.

Қорытынды: Жүргізілген жүйелі шолудың қорытындысы бойынша қуықасты безі қатерлі ісігінің биологиясы мен генетикасын терең түсіну, генетикалық бейіндеу технологиясын пайдалану ауыр аурулармен ауыратын көптеген пациенттердің өмірін сақтап, жақсартуға мүмкіндік береді деп айтуға болады.

Түйінді сөздер: қуықасты безі қатерлі ісігі, ісіктің гетерогендігі, ісіктің микро айналуы, генетикалық бейіндеу.

АННОТАЦИЯ

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Генетика и биология рака предстательной железы: обзор литературы

Актуальность: Несмотря на высокую выживаемость при локализованном раке предстательной железы (РПЖ), метастатический РПЖ остается практически неизлечимым даже после интенсивной мультимодальной терапии. Смертность от запущенного заболевания обусловлена отсутствием терапевтических схем, способных вызывать длительные реакции в условиях крайней гетерогенности опухоли на генетическом и клеточном биологическом уровнях. Эпидемиологические исследования показали, что семейный анамнез злокачественных заболеваний предстательной железы значительно увеличивает риск РПЖ. Во многих случаях клинический диагноз часто основывается на единственной биопсии для определения молекулярного статуса конкретного случая рака. Патологическая и геномная гетерогенность могут приводить к систематическим ошибкам при постановке диагноза. Поэтому использование генетических технологий исследования весьма актуально.

Цель исследования: обосновать использование технологий генетического профилирования в отношении пациентов с РПЖ.

Результаты: Во многих случаях отсутствует многостороннее понимание влияния существующих методов лечения на иммунную систему пациента. Эффективность и переносимость комбинированной терапии зависят от выбора оптимального режима лечения. Необходимо также разработать подходы для определения приоритетов различных видов комбинированной терапии. С учетом того, что геном рака влияет на прогрессирование и течение заболевания, возможно смоделировать эти взаимодействия в условиях генетической модели, что позволит прогнозировать исход и эффективность проводимого лечения.

Заключение: По итогам проведенного систематического обзора можно сказать, что глубокое понимание биологии и генетики РПЖ, использование технологии генетического профилирования дает возможность сохранить и улучшить жизнь многих пациентов с серьезными заболеваниями.

Ключевые слова: Рак предстательной железы (РПЖ), гетерогенность опухоли, микроокружение опухоли, генетическое профилирование.